CALORIC RESTRICTION SENSITIZES MELANOMA TO ANTI-PD-1 IMMUNE CHECKPOINT INHIBITION

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Background Individual response to immune checkpoint inhibition (ICI) in patients with metastatic melanoma varies from 10–40% for monotherapy and 50–60% with combination therapy [1]. Identification of adjuncts to ICI to further bridge treatment response to cure is imperative. We focus on caloric restriction (CR) as an adjunct to anti-PD-1 ICI given its inexpensive nature, relative ease of application, and increased tolerability as compared to fasting.

Methods 12-week C57BL/6J mice were inoculated with Yale University Mouse Melanoma (YUMM 1.7), randomized into diet groups and further randomized into α PD-1 and control (IgG) groups on day 12 (D12). Full diet mice ad lib fed while CR mice were 40% calorically restricted based on average daily food intake. Tumors were measured every 3 days with digital calipers (q3d). α PD-1 or control was intraperitoneally injected starting D12 continuing q3d for 7 injections. Mice were sacrificed and tumors harvested on D31. RNA sequencing was performed on CD45+ CD3+ T cells.

Results Under CR conditions, mice treated with α PD-1 had significantly smaller tumor volumes compared to the full diet cohort treated with α PD-1 (D22, 271.15 m³ vs. 336.72 m³, $p=0.031$) and persisted to harvest (D31, 600.96 m³ vs. 1039.84 m³, $p=0.034$). A significant difference in tumor volumes between CR α PD-1 and CR control treated cohorts was observed starting at D28 (439.34 m³ vs. 667.63 m³, $p=0.005$) and persisted to harvest (D31, 600.96 m³ vs. 884.08 m³, $p=0.009$). However, no significant difference in tumor growth under full diet conditions in murine cohorts treated with α PD-1 or control or separately between CR and full diet cohorts treated with control was observed. On pathway enrichment analysis inflammatory response, cytokine-mediated, response to interferon-gamma, and cell proliferation pathways were downregulated in the CR + α PD-1 cohort. Notable genes found in these pathways include B-cell linker protein (BLNK), tyrosine-protein kinase Lyn (LYN), SYK (spleen tyrosine kinase), toll-like receptor (TLR) TLR4, TLR7, and TLR8.

Conclusions Caloric restriction significantly sensitizes YUMM 1.7 murine melanoma to anti-PD-1 therapy resulting in decreased tumor growth. We show significant modulation of tumor growth in a murine tumor cell line, which has previously demonstrated limited response to α PD-1. In the present study, caloric restriction may decrease inflammation via downregulation of cytokine and toll-like receptor mediated pathways. Furthermore, caloric restriction may reverse the immunosuppressive tumor microenvironment and provide an inexpensive means to increase treatment response to anti-PD-1 therapy.

REFERENCES

1. Ward WH, Farma JM. Cutaneous Melanoma: Etiology and Therapy. Brisbane (AU): Codon Publications. 2017; Chapter 8.

Ethics Approval This study was approved by the University Committee on Animal Resources (UCAR), UCAR-2018-014.

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